REMARKS

The Applicants acknowledge the Examiner's comprehensive Office Action with appreciation. The Office maintains the previously issued Restriction Requirement. Claims 14-26 remain pending in the application; however, Claims 15-22 and 24 have been withdrawn from consideration as a result of the Restriction Requirement. The Office raises rejections under 35 USC § 102 and 35 USC § 103. The Office also raises an obviousness-type double patenting rejection.

Claims 14, 23, and 25-26 are rejected under 35 USC § 102(b) as being anticipated by Vincent, et al. (US Patent No. 4,914,214). It is the position of the Office that Vincent, et al. disclose (at Column 10) perindopril t-butylamine salt in crystalline form and that the disclosed compound anticipates the instant α-crystalline form of perindopril t-butylamine salt.

Claims 25 and 26 are also rejected under 35 USC § 102(e) as being anticipated by Guez, et al. (US Patent No. 6,653,336). It is the position of the Office that Guez, et al. disclose a pharmaceutical composition tablet comprising perindopril t-butylamine salt and a diuretic, such as indapamide, and that the disclosed pharmaceutical composition anticipates the instant pharmaceutical composition comprising the instant α-crystalline form of perindopril t-butylamine salt and a diuretic, including indapamide.

The Office states that the only difference between the instant claims and the cited references is that Vincent, et al. and Guez, et al. are silent with respect to X-ray diffraction data, and it is the position of the Office that the claimed X-ray diffraction data associated with the α-crystalline form of perindopril t-butylamine salt has no patentable weight. While the Office provides no legal or other explanation for this conclusion, the Applicants speculate that it may be the position of the Office that the claimed X-ray diffraction characteristics are inherent to the compounds disclosed in Vincent, et al. and Guez, et al. With this understanding, the Applicants respond as follows.

The Applicants respectfully submit that perindopril t-butylamine salt disclosed in Vincent, et al. is crystallized directly from the reaction mixture, in contrast to the instant α-crystalline form, which is produced by heating a solution of perindopril t-butylamine salt to reflux in ethyl acetate and then gradually cooling until crystallization is complete. Thus, although the Vincent, et al. reference discloses perindopril t-butylamine salt, it does not disclose or suggest the instant α-crystalline form. See Vincent, et al. at column 9 (step 3D) wherein the isolation procedure is described as cooling the reaction mixture and then filtering off the product.

Moreover, the Applicants respectfully submit that, according to MPEP § 2112, in order to rely on a theory of inherency, the Office must provide "a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." MPEP § 2112 also states that "the fact that a certain result or characteristic may occur or be present in the prior art is not enough to establish the inherency of that result or characteristic." As noted above, the Office has provided no support for the anticipation conclusion.

With this Response, the Applicants provide and make reference to International Published Application WO 2005/037788 (Singh, et al.) which discloses (at page 15, paragraph 2 and page 19, paragraph 4) that by reproducing the process for making perindopril t-butylamine salt disclosed in US Patent No. 4,914,214 (Vincent, et al.), in particular step 3D at column 9, a product other than the α-crystalline form disclosed in International Published Application WO 01/87835 (an International equivalent of the instant application) is obtained. In other words, one skilled in the art has already published empirical data which rebuts the Office speculation.

In fact, step 3D of Vincent, et al. only discloses that tert-butylamine is added gradually, that refluxing is carried out until dissolution is complete, and that filtration, cooling, filtration and drying are carried out to produce perindopril t-butylamine salt. There is no disclosure with respect to the various possibilities for the cooling step, which could be, for example, rapid cooling or stepwise cooling.

The Applicants also provide a Declaration by Dr. Gérard COQUEREL, a scientist skilled in this particular art, which speaks to the 102/103 rejection. Specifically, the Declarant provides data which demonstrate and confirm that the instant α-crystalline form is novel and non-obvious based on the cited references.

The Declarant has reproduced step 3D of Vincent, et al. (Experiment 1). The X-ray diffraction spectrum of the product obtained by the process disclosed in Vincent, et al. is different than the X-ray diffraction spectrum of the instant α-crystalline form, demonstrating that the structure of the product of Vincent, et al. does not correspond to the instant α-crystalline form.

Guez, et al. disclose pharmaceutical compositions comprised of perindopril and indapamide; however, Guez, et al. do not disclose that the perindopril t-butylamine salt used in the disclosed pharmaceutical compositions is in crystalline form, much less the instant α-crystalline form. Thus, the Office has not demonstrated that the "allegedly inherent characteristic" necessarily flows from the teaching of the cited reference, and there is no disclosure in the Guez, et al. reference which suggests a pharmaceutical composition comprising the instant α-crystalline form. The above-noted demonstrations establish that there is no prior disclosure of an α-crystalline form of perindopril, and therefore, Guez, et al. could not possibly disclose or suggest the instant composition.

Therefore, the Applicants respectfully submit that the instant α-crystalline form of perindopril t-butylamine salt and its pharmaceutical compositions are not anticipated by the respective disclosures of the Vincent, et al. and Guez, et al., references. Reconsideration and withdrawal of the anticipation rejections is respectfully requested.

Claims 14, 23, and 25-26 are further rejected for obviousness under 35 USC § 103(a) based on Vincent, et al. in view of Guez, et al. It is the position of the Office that, since Vincent, et al. disclose a crystalline form of perindopril t-butylamine salt and Guez, et al. disclose a pharmaceutical composition comprising perindopril t-butylamine salt and a diuretic, such as indapamide, it would have been obvious to

one skilled in the art to employ the compounds/compositions of Vincent, et al. and Guez, et al. to obtain the instant α-crystalline form of perindopril t-butylamine salt and its pharmaceutical compositions.

The Office also states (at pages 7-8 of the instant Office Action, citing In re Cofer, 148 USPQ 268 (CCPA)) that "...changing the form purity or other characteristic of an old product does not render the novel form patentable where the difference in form, purity, or characteristic was inherent in or rendered obvious by the prior art." The Office goes on to state that, according to MPEP § 2112, "something which is old does not become patentable upon the discovery of a new property."

As noted above with respect to the anticipation rejection, MPEP § 2112 also states that "the fact that a certain result or characteristic may occur or be present in the prior art is not enough to establish the inherency of that result or characteristic." Moreover, the Applicants respectfully submit that one skilled in the art would recognize that, it is necessary, in order to obtain a polymorphic form, to select from the following:

- the solvent, from a range of possible solvents selected from:
    - polar solvents,
    - non-polar solvents,
    - hydrophilic solvents and
    - hydrophobic solvents;
- the temperature, from various temperatures;
- the cooling of solutions: for example, rapid, slow, stepwise;
- the optional addition of a second solvent;
- the stirring: for example, yes, no, vigorous;
- the heating;
- the sublimation;
- the adjustment in pH: for example, rapid or slow.

There is no disclosure in the cited references which would suggest to one skilled in the art that the conditions which are disclosed and claimed in the present application, rather than any other possible conditions, would produce the instant

α-crystalline form. Clearly, the selection of the particular conditions for the isolation of the instant crystalline form would require extensive experimentation through trial and error.

Experiments 2 and 3 of the COQUEREL Declaration demonstrate the superior characteristics associated with the instant α-crystalline form. The instant α-crystalline form is in the form of individual needles having a homogeneous distribution, which allows especially efficient filtration and drying as well as especially uniform and reproducible pharmaceutical formulation, and which form is more stable than the perindopril t-butylamine salt produced by the process of Vincent, et al.

As disclosed in the instant specification, as well as in the COQUEREL Declaration, the instant α-crystalline form provides the tert-butylamine salt of perindopril in a form that is sufficiently stable to allow it to be stored for a prolonged period, that is perfectly reproducible and that is easily formulated.

Moreover, the Applicants respectfully submit that, in the CCPA decision (In re Cofer) cited in the instant Office Action at pages 8 and 10, the CCPA held that

> [W]hether a given chemical compound or composition has the same usefulness as closely related materials may be an important consideration in determining obviousness under 35 USC 103. But it is only one consideration. We think the board failed to address itself to other factors which must be given weight in determining whether the subject matter as a whole would have been obvious, namely, whether the prior art suggests the particular structure or form of the compound or composition as well as suitable methods of obtaining that structure or form. The new form of the compound set forth in the claims is as much a part of the "subject matter as a whole" to be compared with prior art as are other properties of the material which make it useful.

Therefore, notwithstanding the instant demonstration of the superior and unexpected properties associated with the instant α-crystalline form provided in the COQUEREL Declaration, the Applicants further submit that the Office has not made the required

demonstration, i.e., that the cited references teach or suggest "the particular structure or form" of the instant α-crystalline form as well as "suitable methods of obtaining that structure or form" to establish a case of *prima facie* obviousness.

The Applicants also respectfully submit that in two non-precedential decisions by the BPAI (Ex Parte Gala and Dibenedetto – Appeal No. 2001-0987; Application 09/169,109 and Ex Parte Havens – Appeal No. 2001-0091; Application No. 08/732,254), the Board found that a new crystalline form was not anticipated nor rendered obvious by either the earlier disclosure of another distinct polymorph (Ex Parte Gala and Dibenedetto) or the compound *per se* (Ex Parte Havens). These recent decisions, although non-precedential, are consistent with the holding in Cofer.

Thus, the Applicants respectfully submit that the instant α-crystalline form as well as the instant pharmaceutical compositions comprising the α-crystalline form are not rendered obvious by the disclosure of the Vincent, et al. and Guez, et al. references. Reconsideration and withdrawal of the obviousness rejection is respectfully requested.

Claims 14, 23, and 25-26 are also provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1,9, and 11-12 of co-pending application US Serial No. 11/052,489. It is the position of the Office that, although the conflicting claims are not identical, they are not patentably distinct since the instant claims as well as the claims in the co-pending application are directed to a crystalline form of perindopril t-butylamine salt.

The Applicants respectfully submit that one skilled in the chemical arts would recognize that compound such as perindopril may exist in distinct crystalline forms (i.e., polymorphs). One skilled in the art would also recognize that different, crystalline forms of the compound would possess distinct physical properties. It has already been established by the discussion above that the Office and the courts recognize that distinct crystalline forms may represent patentably distinct subject matter. Moreover, there is nothing in co-pending application US Serial No. 11/052,489 to suggest the particular α-crystalline form nor a suitable method for

obtaining the instant α-crystalline form. Thus, the instant α-crystalline form of perindopril t-butylamine salt is patentably distinct from the limited disclosure of the β-crystalline form of perindopril t-butylamine salt. Reconsideration and withdrawal of the obviousness-type double-patenting rejection is respectfully requested.

Finally, the Applicants request rejoinder of dependent species and method claims upon the identification of a patentable genus.

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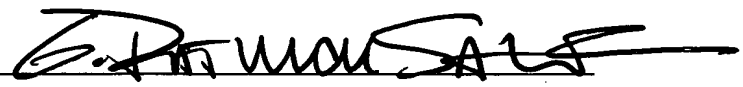
Accordingly, entry of the COQUEREL Declaration, reconsideration of all grounds of objection and rejection, withdrawal thereof, and passage of this application to issue are all hereby respectfully solicited.

It should be apparent that the undersigned attorney has made an earnest effort to place this application into condition for immediate allowance. If he can be of assistance to the Examiner in the elimination of any possibly-outstanding insignificant impediment to an immediate allowance, the Examiner is respectfully invited to call him at his below-listed number for such purpose.

Allowance is solicited.

Respectfully submitted,

THE FIRM OF HUESCHEN AND SAGE

By: 

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Enclosure: COQUEREL Declaration; Form PTO-1449 and Accompanying References; and Postal Card Receipt

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